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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/476,253	12/30/1999	JOHN W. WATSON	PC9731A	7551

23913 7590 07/28/2005

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EXAMINER	
STITZEL, DAVID PAUL	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/476,253	WATSON ET AL.	
	Examiner	Art Unit	
	David P. Stitzel, Esq.	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-10,16-18,20,25-29,31,36-39 and 42-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-10,16-18,20,25-29,31,36-39 and 42-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/13/00; 6/18/2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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Official Action

Acknowledgment of Receipt

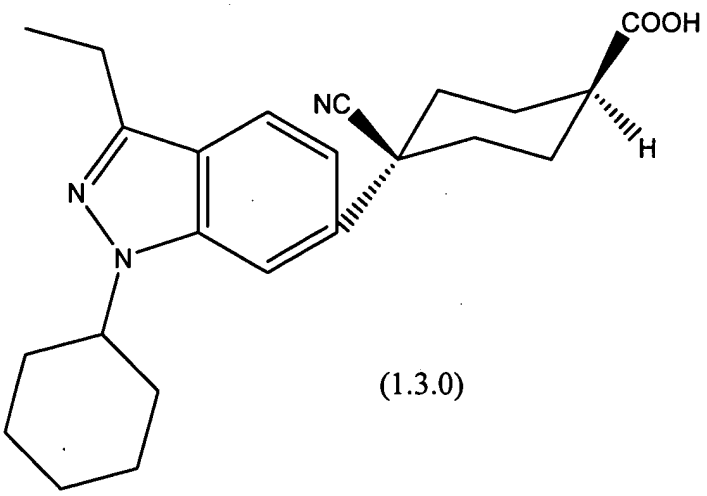
Receipt of the Applicants' Election, with traverse, of Group I encompassing claims 1-10, 12-15, 28-29, 31-39 and 44, which was filed on April 12, 2004 in response to the restriction requirement as set forth in the Official Action mailed on March 23, 2004, is acknowledged. Upon consideration of the aforementioned restriction requirement, claims 16-18, 20, 25-27 and 42-43, which were previously withdrawn from consideration as a result of said restriction requirement, are herby rejoined under 37 C.F.R. § 1.104. Since all of the claims that were previously withdrawn from consideration under 37 C.F.R. § 1.142 have been rejoined, the aforementioned restriction requirement made in the above referenced Official Action is hereby withdrawn.

Status of Claims

Claims 3-6, 12-15, 21-24 and 32-35 were withdrawn from consideration by the Applicants' Election, without traverse, of claims 1-2, 7-11, 16-20, 25-31 and 36-41 for further prosecution, which was filed on September 10, 2001 in response to the restriction requirement as set forth in the Official Action mailed on July 5, 2001. In addition, claims 40 and 41 were canceled by an amendment, which was filed on June 18, 2002, in response to the Official Action that was mailed on April 23, 2002. Furthermore, claims 11, 19 and 30 were canceled and replaced by new claims 42, 43 and 44, respectively, via an amendment, which was filed on November 24, 2003 in response to the Office Action that was mailed on May 21, 2003. As previously mentioned, claims 16-18, 20, 25-27 and 42-43 have been rejoined. As a result, claims 1-2, 7-10, 16-18, 20, 25-29, 31, 36-39 and 42-44 are currently pending and therefore examined herein on the merits for patentability.

Clarification of Elected Species

In the Applicants' second Supplemental Response, which was filed on June 18, 2002, to the restriction requirement, as set forth in the Official Action mailed on July 5, 2001, Applicants explicitly "elected the species of Formula (1.3.0)":



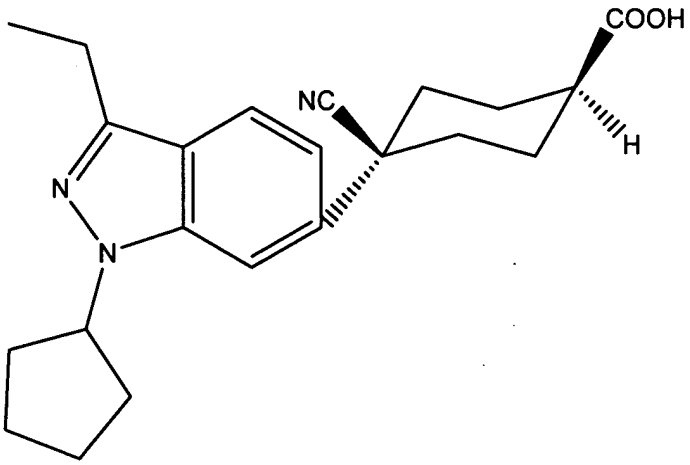
(1.3.0)

(1*s*,4*s*)-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid

which is set out on page 71 of the instant specification." The corresponding chemical name to the aforementioned Formula (1.3.0) is also provided on page 39 (line 28) of the instant specification, in addition to the *ninth* recited species in claims 10 and 39, as "cis-4-cyano-4-(1-cyclo*hexyl*-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid," which is also known in the scientific chemical literature as "(1s,4s)-4-cyano-4-(1-cyclohexyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid."

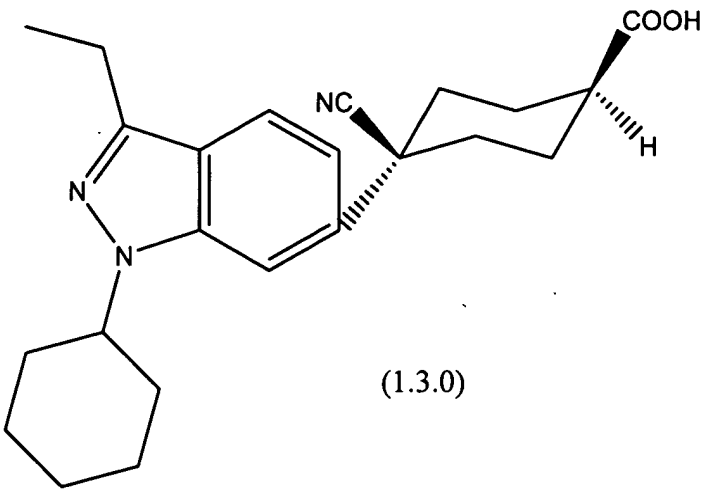
Unfortunately however, Applicants muddy the water by further elaborating in the same second Supplemental Response that "in claims 10 and 39 the elected species is the *fifth* recited species in each said claim, i.e., 'cis-4-cyano-4-(1-cyclo*pentyl*-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid'." (Emphasis added). In addition to the fifth recited element in claims 10 and 39, "cis-4-cyano-4-(1-cyclopentyl-3-ethyl-

1*H*-indazol-6-yl)cyclohexanecarboxylic acid" is also provided on page 39 (line 22) of the instant specification. To digress for a moment, the structural formula for cis-4-cyano-4-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid, also known in the scientific chemical literature as "(1s,4s)-4-cyano-4-(1-cyclopentyl-3-ethyl-1H-indazol-6-yl)cyclohexanecarboxylic acid," is as follows:



(1*s*,4*s*)-4-cyano-4-(1-cyclopentyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid

Numerous unsuccessful attempts were made on Thursday, July 7, 2005, as well as on Friday, July 8, 2005, to contact the attorney of record (Mr. Raymond M. Speer, Esq.) telephonically (212-733-4606) to clarify the aforementioned discrepancy. As a result, in an effort to further the goal of expeditious and compact prosecution, based upon the Applicants' explicit election of the "species of Formula (1.3.0)," the chemical structure of which is as follows:



(1.3.0)

(1*s*,4*s*)-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid

the Examiner will assume that *cis*-4-cyano-4-(1-cyclo*hexyl*-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid (and not *cis*-4-cyano-4-(1-cyclo*pentyl*-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid; *trans*-4-cyano-4-(1-cyclo*hexyl*-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid; or *trans*-4-cyano-4-(1-cyclo*pentyl*-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid) is in fact the Applicants' intended elected species. Despite the aforementioned assumption however, Applicants' clarification of this issue is respectfully requested.

Claim Rejections - 35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112, which forms the basis of the claim rejections as set forth under this particular section of the Official Action:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 7-9, 16-18, 20, 25-29, 31, 36-38 and 42-44 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a reasonable subgenus around the thirty specific chemical derivatives exemplified in claims 10 and 39, wherein the following chemical properties are reasonably maintained: total molecular size; charge distribution; hydrophobicity; polarity; hydrophilicity; and hydrogen bonding, for example (CAUTION: Said subgenus must have adequate written description in the specification or it may create an issue of new matter), does not reasonably provide sufficient enablement to one of ordinary skill in the art as to which of the seemingly infinite number of derivatives disclosed across the entire scope of the extremely generic claims would in fact actually inhibit *phosphodiesterase-4 (PDE4), including all isozyme subtypes thereof* (specification: page 11, lines 21-23; and page 56, lines 2-3), sufficient to restore normal gastric motility, without an undue amount of experimentation. In addition, the specification merely discloses, without more, that an assay *may* be performed to determine the inhibiting activities and specificities of the synthesized PDE4 isozyme inhibitors (specification: page 56, lines 33-34; page 57, lines 1-2; page 62, lines 14-34; and page 63, lines 1-18), without providing a scintilla of scientific data illustrating that even a single synthesized PDE4 isozyme inhibitor does in fact actually exhibit inhibitory properties against even a single PDE4 isozyme type or subtype thereof, sufficient to restore normal gastric motility. Moreover, without scientific data illustrating structure-activity relationships, with respect to how the substitution of the indazole with various particular chemical moieties directly effects the bioactivity and inhibitory properties against PDE4 isozyme subtypes thereof, one of ordinary skill in the art would not be able to reasonably predict which of the vast number of derivatives disclosed across the full scope of the extremely generic claims would in fact actually exhibit inhibition against even a single PDE4 isozyme subtype thereof, sufficient to restore normal gastric motility, without an undue amount of experimentation.

Therefore, the specification does not enable one skilled in the relevant art to which the invention pertains to practice (i.e., use) the invention commensurate in scope with the aforementioned rejected claims.

Unlike the tremendously broad claims discussed hereinabove, claims 10 and 39 are admittedly more narrowly defined by being collectively directed to only thirty (30) particular embodiments, or specific chemical derivatives, of the general formula comprising a substituted indazole for restoring normal gastric motility by inhibiting PDE4 isozyme subtypes thereof. In addition, the specification also provides numerous synthetic schemes sufficient to enable one skilled in the art to practice (i.e., make) the specific chemical derivatives. Unfortunately however, although chemical names are provided for each of the thirty specific chemical derivatives disclosed in claims 10 and 39, the corresponding chemical structures for each of the named specific chemical derivatives are not disclosed. This deficiency can apparently lead to confusion, even to those skilled in the art, as evidenced above by the applicants' own confusion as to what chemical structure is an accurate and proper representation of its corresponding chemical name. Furthermore, the specification utterly fails to provide an iota of scientific data illustrating that even one of the thirty specifically named PDE4 isozyme inhibitor derivatives does in fact actually exhibit inhibition against even a single PDE4 isozyme subtype thereof, sufficient to restore normal gastric motility. If the thirty specifically named PDE4 isozyme inhibitor derivatives do in fact actually inhibit PDE4, sufficient to restore normal gastric motility as claimed, then the specification would be enabling for a reasonable subgenus around the thirty specific chemical derivatives exemplified in claims 10 and 39, wherein the following chemical properties are reasonably maintained: total molecular size; charge distribution; hydrophobicity; polarity; hydrophilicity; and hydrogen bonding, for example.

An analysis of whether the scope of a particular claim is actually supported by the disclosure in a patent application requires a determination of whether the disclosure, at the time of filing, contained

sufficient information regarding the subject matter of the claim at issue so as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Wands*, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988). Therefore, the test of enablement is not whether experimentation is necessary, but rather, if experimentation is in fact necessary, whether it is reasonably considered to be undue. *In re Angstadt*, 190 USPQ 214, 219 (CCPA 1976).

Determining the issue of enablement with respect to a claim is a question of law based on underlying factual findings. *In re Vaeck*, 20 USPQ 2d 1438, 1444 (Fed. Cir. 1991). More particularly, there are many factors to be considered in determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, and whether any necessary experimentation is reasonably considered to be "undue." See *In re Wands* at page 1404. MPEP § 2164.01(a). The Court in *In re Wands* set forth the following factors to be considered, which include, without limitation, the: 1. scope or breadth of the claims; 2. nature of the invention; 3. relative level of skill possessed by one of ordinary skill in the art; 4. state of, or the amount of knowledge in, the prior art; 5. level or degree of predictability, or a lack thereof, in the art; 6. amount of guidance or direction provided by the inventor; 7. presence or absence of working examples; and 8. quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure.

The determination that "undue" experimentation would have been needed to make and use the claimed invention is not a simple *ad hoc* determination substantiated by only a single factual determination, but rather, a well-grounded conclusion resulting from a weighing of all of the aforementioned factual considerations. *Id.* That is, it is improper to conclude during examination that a claim is not enabled based upon a scant analysis of only a single factor while ignoring one or more of the remaining factors. *Id.* at page

1407. Therefore, the examiner must consider all of the evidence related to each of the aforementioned factors and any conclusion of a lack of enablement must be supported by the evidence as a whole. *Id.*

1. The Scope or Breadth of the Claims

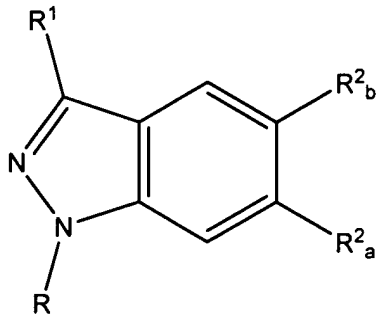
All questions of enablement are evaluated against the claimed subject matter. MPEP § 2164.08. Therefore, the focus of the examination inquiry is whether everything within the scope of the claim is enabled by the supporting disclosure. *Id.* Accordingly, the first analytical step requires that the examiner determine the exact breadth of the subject matter encompassed by the claims with respect to the supporting disclosure. *AK Steel Corp. v. Sollac*, 68 USPQ 2d 1280, 1287 (Fed. Cir. 2003).

The Federal Circuit has repeatedly held that "***the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'***." (Emphasis added). *In re Wright*, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993). These holdings are necessitated by the fact that one of ordinary skill in the art does not look to the claims, but rather to the specification, to determine how to practice the claimed invention. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 220 USPQ 303, 316-317 (Fed. Cir. 1983). The teachings of the specification must not be ignored when analyzing the enabled scope of a claim, as the claim is to be interpreted in light of the specification by giving said claim its broadest reasonable interpretation that is consistent with the specification. *Raytheon Co. v. Roper Corp.*, 220 USPQ 592, 597 (Fed. Cir. 1983), cert. denied, 469 U.S. 835 (1984).

The scope or breadth of the claims was a factor considered and discussed at length by the Court in *Amgen v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991), cert. denied, 502 U.S. 856 (1991), wherein the Court stated, in relevant part, that:

> Amgen has not enabled preparation of DNA sequences sufficient to support its all-encompassing claims. Despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. This disclosure might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them.

In the instant case, independent claims: 1 (dependent claims: 2, 7-10 and 28-29); 42 (dependent claims: 16-18); 43 (dependent claims: 20 and 25-27); and 44 (dependent claims: 31 and 36-39), along with their aforementioned corresponding dependent claims, are directed to a substituted indazole for restoring normal gastric motility by exhibiting inhibition of PDE4, including all isozyme subtypes thereof, said substituted indazole comprising a general formula:



(IA)

wherein independent claims 1, 42, 43 and 44, which are breathtakingly immense in scope and collectively span over ninety-one (91) entire pages in length, are solely directed to defining a seemingly infinite number of various chemical moieties that may constitute not only the pendant R, R^1, R^2_a and R^2_b groups, but also R^{500} potential substituents thereof. In addition, claims 1, 42, 43 and 44 are extremely broad in scope in that there are numerous isozyme subtypes of PDE4 (specification: page 11, lines 21-23; and page 56, lines 2-3).

It is readily apparent from a practical examination standpoint that an examiner faced with the conundrum of conducting a thorough search in the prior art would quickly become overwhelmed, especially when taking into consideration the countless number of various substituted indazole derivatives that may be synthesized by systematically modifying the plethora of various chemical moieties that may constitute not only the pendant R, R^1, R^2_a and R^2_b groups, but also R^{500} potential substituents thereof.

In stark contrast to the expansive breadth of the independent claims discussed hereinabove, claims 10 and 39 are admittedly more narrowly defined by being collectively directed to thirty (30) specific chemical derivatives of the aforementioned general formula comprising a substituted indazole.

2. The Nature of the Invention

The "nature of the invention" refers to the subject matter to which the claimed invention pertains. MPEP § 2164.05(a). The nature of the invention becomes the backdrop for determining the relative level of skill possessed by one of ordinary skill in the art, as well as the state of the prior art. *Id.*

In the instant case, the nature of the invention is directed to a substituted indazole for restoring normal gastric motility by exhibiting inhibition against PDE4, including all isozyme subtypes thereof.

3. The Relative Level of Skill Possessed by One of Ordinary Skill in the Art

The relative level of skill possessed by one of ordinary skill in the relevant art to which the claimed invention pertains is determined as of the effective filing date of the application. MPEP § 2164.05(b).

The relative level of skill possessed by one of ordinary skill in the art of inhibiting PDE4 isozymes for the treatment of gastroparesis, or gastric hypomotility, as well as diabetes mellitus, is relatively high, as a majority of lead investigators conducting scientific research in this particular technological area, as of the effective filing date of the instant application, possess a Ph.D. in a scientific discipline such as chemistry, biochemistry, biology or the like.

4. The State of the Prior Art

The "state of the prior art" refers to what one of ordinary skill in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. MPEP § 2164.05(a). It should be noted that the state of the prior art also provides evidence for, and is directly proportional to, the level or degree of predictability in the art. *Id.* On the other hand, the state of the prior art is inversely related not only to the amount of guidance or direction that is required in the specification as filed, but also to the need that working examples be present in the specification as filed. *Id.*

As a general rule, publications that are publicly first disclosed after the effective filing date of a patent application generally should not be used to show what was known by one of ordinary skill in the art at the time the application was filed. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). However, an exception to the aforementioned general rule could occur in the event that a reference, having a post-filing publication date, provides evidence as to what one of ordinary skill in the art would have known on or before the effective filing date of the patent application. *In re Hogan*, 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). For example, the Court in *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) held, in relevant part, that:

> An article published five (5) years after the effective filing date of the patent application adequately supported the patent examiner's position that the physiological activity of certain viruses was sufficiently unpredictable such that a person of ordinary skill in the art on or before the effective filing date of the patent application would not have reasonably believed that the success of one particular virus with one particular animal could reasonably and successfully be extrapolated to include all viruses with all living organisms. As a result, the claims that were not explicitly directed to the specific virus and the specific animal were subsequently held to be nonenabled.

As discussed hereinbelow in greater detail, an extraordinary degree of unpredictability, not to mention a great deal of uncertainty due to a distinct lack of knowledge of the skilled artisan, existed in the state of the prior art regarding how the modification of various chemical substituents associated with previously known PDE4 inhibitors would affect the inhibitory characteristics thereof.

*5. **The Level or Degree of Predictability, or a Lack Thereof, in the Art***

The state of the prior art provides evidence for, and is directly proportional to, the level or degree of predictability in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). MPEP §§ 2164.03, 2164.05(a). In other words, the more that is known by one of ordinary skill in the art at the time the application was filed about the subject matter to which the claimed invention pertains, including how to make and use the invention, the higher the level or degree of predictability in the art. *Chiron Corp. v. Genentech Inc.*, 70 USPQ 2d 1321, 1326 (Fed. Cir. 2004). Therefore, the level or degree of "predictability or a lack thereof" in the art refers to the ability of one skilled in the art to extrapolate and thus readily anticipate the effect of a change within the disclosed subject matter to which the claimed invention pertains. *In re Marzocchi*, 169 USPQ 367, 369-70 (CCPA 1971). On the other hand, if one of ordinary skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is a lack of predictability in the art. See *In re Marzocchi* at pages 369-370.

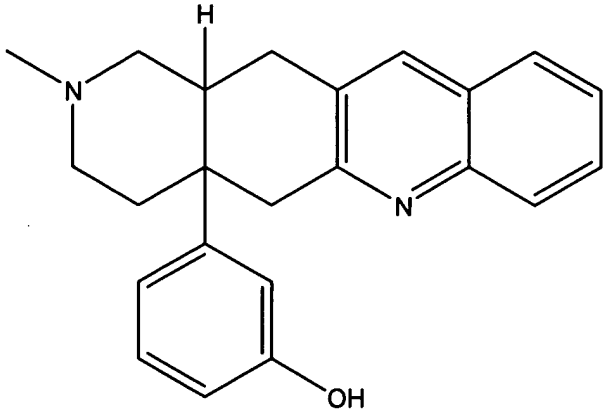
While a disclosure of each and every operable species claimed is not required, in patent applications containing claimed subject matter that is directed to the biotechnology, chemical and pharmaceutical arts, where the results are unpredictable, the disclosure within the specification of a single species usually does not provide an adequate basis to support the generic claims, as more is typically required. *In re Vickers*, 61 USPQ 122, 127 (CCPA 1944); and *In re Fisher*, at 24. This is particularly the case when it is not readily apparent from the disclosure of a particular species, what other species will work. MPEP §§ 2164.03.

Drug discovery remains extremely tedious, laborious and expensive. For example, it is not all that uncommon for a pharmaceutical company to spend over one billion dollars in research and development, as well as clinical testing, before even a single drug sees the light of day in the marketplace, only then allowing said company the opportunity to begin recouping their investments for not only the successful drug, but also the countless other drugs that failed. Despite recent advancements in the sophistication of drug discovery instrumentation and techniques, an extraordinary degree of unpredictability still remains in the biotechnology, chemical and pharmaceutical arts, therefore requiring continued trial and error experimental research. The basis for the extraordinary degree of unpredictability associated with drug discovery in particular, can be attributed to the exquisite stereospecificity that exists between an enzyme and its corresponding substrate, or a ligand and its corresponding receptor. This principle is particularly evidenced by the following examples previously documented in the biotechnology, chemical and pharmaceutical scientific literature and prior art.

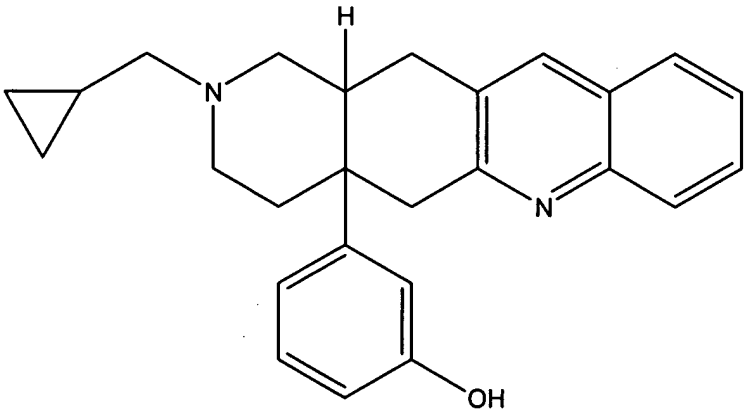
It is known in the biotechnology art that aminoacyl-tRNA synthetases exhibit an extremely high degree of stereospecificity with respect to their ability to discriminate between D- and L-optical isomers and between amino acids that are simple one carbon homologs of one another (i.e., aspartic acid versus glutamic acid), as well as between amino acids that are simply molecular isomers (i.e., leucine versus isoleucine)." Francklyn, C., Aminoacyl-tRNA Synthetases: Versatile Players in the Changing Theater of Translation, RNA, Vol. 8, pp. 1363-1372 (2002). It is also known that vertebrate growth hormone, which consists of 198 amino acids in length, transforms from being an agonist to an antagonist when a single amino acid is changed. U.S. Patent Number 5,350,836, which issued to Kopchick, et al. on September 27, 1994. It is further known that a majority of key therapeutics specifically act on particular cell surface receptors, for example: migraine drugs act on dopaminergic receptors; allergy drugs act on histamine receptors; asthma

and blood pressure drugs act on adrenergic receptors; anti-depressive and anti-compulsive drugs act on serotonin receptors; and anti-anxiety drugs act on both serotonin receptors, as well as GABA receptors. For a general overview of the aforementioned cell surface receptors, see the relevant chapters and subheadings within Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., McGraw-Hill, NY, (1996).

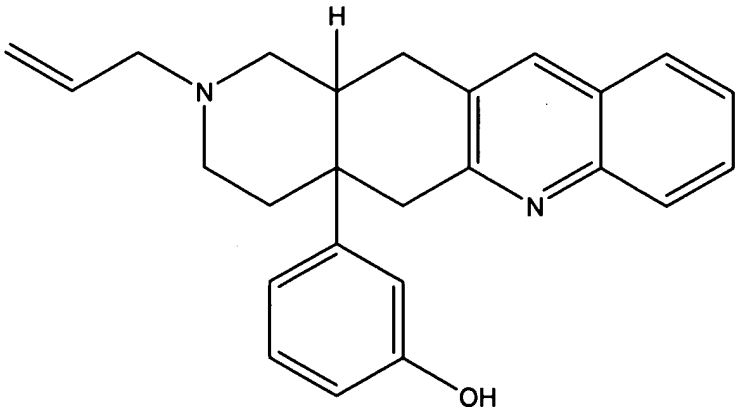
The unpredictable and surprisingly dramatic effects that can result from a simple modification of even a single pendant chemical moiety of an active core compound is strikingly apparent when considering opioid analgesics, for example. Upon simple substitution of the N-methyl group of TAN-67 (illustrated hereinbelow), which is a highly selective and potent nonpeptidic δ opioid receptor *agonist*, with either a methylcyclopropyl group, or even an allyl group for that matter, TAN-67 is subsequently converted into a δ opioid receptor *antagonist*! Goodman & Gilman's The Pharmacological Basis of Therapeutics, 9th Ed., McGraw-Hill, NY, page 549 (1996); and Nagase, H., et al., The Pharmacological Profile of δ Opioid Receptor Ligands, (+) and (-) TAN-67 on Pain Modulation, Life Sciences, Vol. 68, pp. 2227-2231 (2001).



3-(1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol (a.k.a. TAN-67)
delta opioid receptor ***agonist***

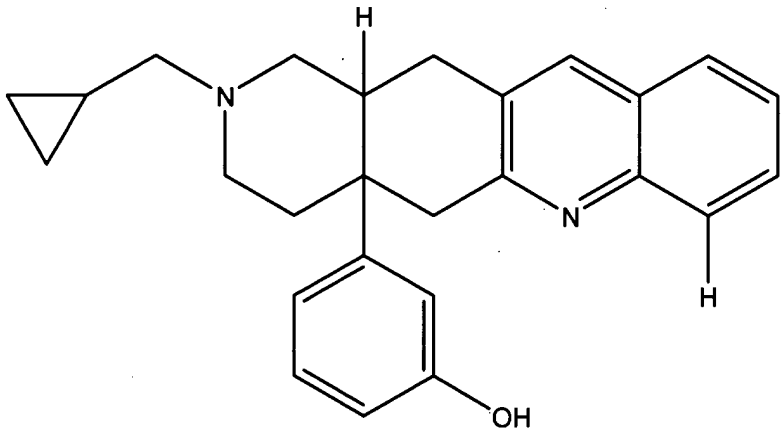


3-(2-(cyclopropylmethyl)-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

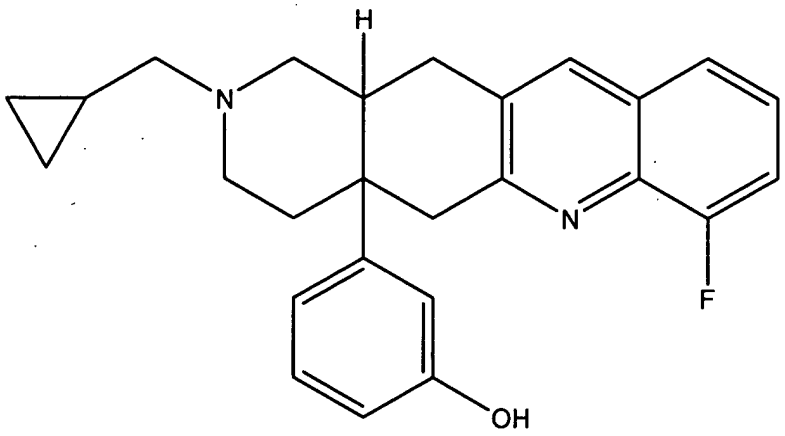


3-(2-allyl-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***

In addition, if one were to modify the methylcyclopropyl substituted TAN-67, which is a δ opioid receptor *antagonist*, by substituting a fluorine atom for a hydrogen atom on the aromatic phenyl ring near the quinoline nitrogen (illustrated hereinbelow), the δ opioid receptor *antagonist* would be converted into a *partial* δ opioid receptor *agonist*, even though fluorine and hydrogen have the same atomic radius!!



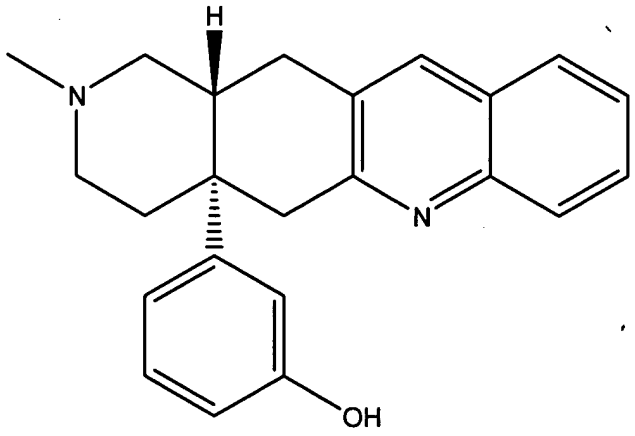
3-(2-(cyclopropylmethyl)-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
delta opioid receptor ***antagonist***



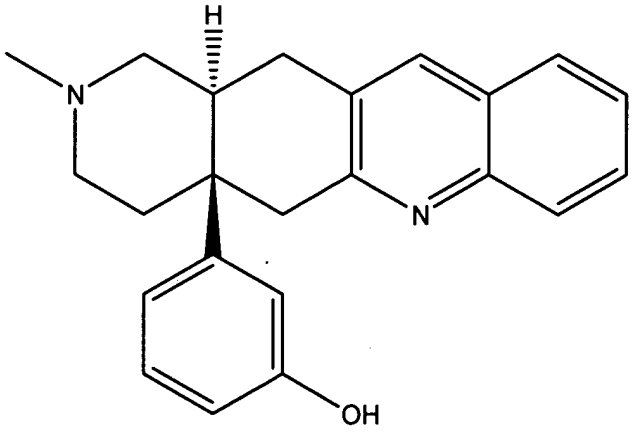
3-(2-(cyclopropylmethyl)-7-fluoro-1,2,3,4,4a,5,12,12a-octahydropyrido[3,4-*b*]acridin-4a-yl)phenol
partial delta opioid receptor ***agonist***

Moreover, by simply selecting from different stereoisomers of TAN-67 (illustrated hereinbelow), one could go from (-)TAN-67, which is a potent antinociceptive (analgesic), to (+)TAN-67, which not only fails

to exhibit analgesic properties, but astonishingly induces pain-like nociceptive behavior, such as scratching and biting!!!



3-((4a*S*,12a*R*)-1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol
(a.k.a. (-)TAN-67)
potent antinociceptive (analgesic)



3-((4a*R*,12a*S*)-1,2,3,4,4a,5,12,12a-octahydro-2-methylpyrido[3,4-*b*]acridin-4a-yl)phenol
(a.k.a. (+)TAN-67)
induces pain-like nociceptive behavior

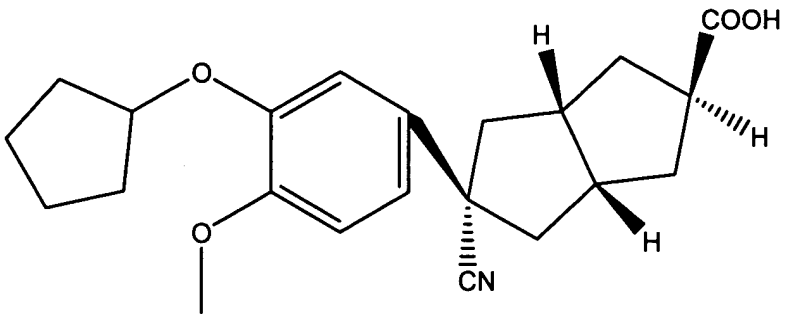
Based on the aforementioned discussion regarding opioid analgesics, it is readily apparent that minor, seemingly trivial, modifications to the core compound can create profound changes in biological activity.

The paramount and unpredictable ramifications that minor structural modifications to the core compound can have on the biological activity of opioid receptors are equally pertinent and applicable to the development of agonists and antagonists of all receptors. Therefore, this example illustrates the exquisite stereospecific characteristics associated with all therapeutic receptor agonists and antagonists.

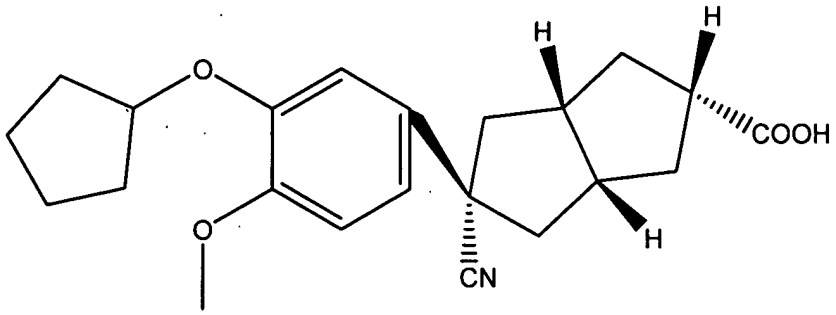
A final example evidencing unpredictability in association with drug discovery is illustrated by the following research efforts, which utilized combinatorial chemistry techniques. Combinatory chemistry is generally defined as a branch of applied chemistry concerned with the rapid synthesis and screening of large numbers of different but related chemical compounds generated from a known building block in order to recover new substances optimally suited for a specific function. In this particular example, combinatorial chemistry techniques were implemented in an effort to identify more efficacious inhibitors of cathepsin D, which is an aspartyl protease. Kick, E.K., et al., Structure-Based Design and Combinatorial Chemistry Yield Low Nanomolar Inhibitors of Cathepsin D, Chemistry & Biology, Vol. 4, No. 4, pp. 297-307 (1997). More specifically, combinatorial libraries were designed and created around the synthesis and subsequent structural derivatization of a stable mimetic building block of the tetrahedral intermediate of amide hydrolysis, namely (hydroxyethyl)amine isostere, which was an already known inhibitor of aspartyl proteases. Of the 2,000 derivatives that comprised the resultant and expansive library, over 90% of the synthesized compounds were biologically *inactive*. Since more than 90% of the synthesized compounds generated in the aforementioned combinatorial library, which was designed and created around the structural derivatization of a stable and efficacious building block or active core, were in fact biologically *inactive*, one of ordinary skill in the art would have a justifiably sound reason to doubt that even a reasonable fraction, much less a simple majority, of the chemical derivatives disclosed across the entire scope of the tremendously broad and extremely generic claims would in fact possess desired biological activity. With

such a high degree of unpredictability in the drug discovery art, the applicant bears a greater burden of providing adequate support in the specification so as to guide one of ordinary skill in the art through the generic maze that is commensurate in scope with the claims.

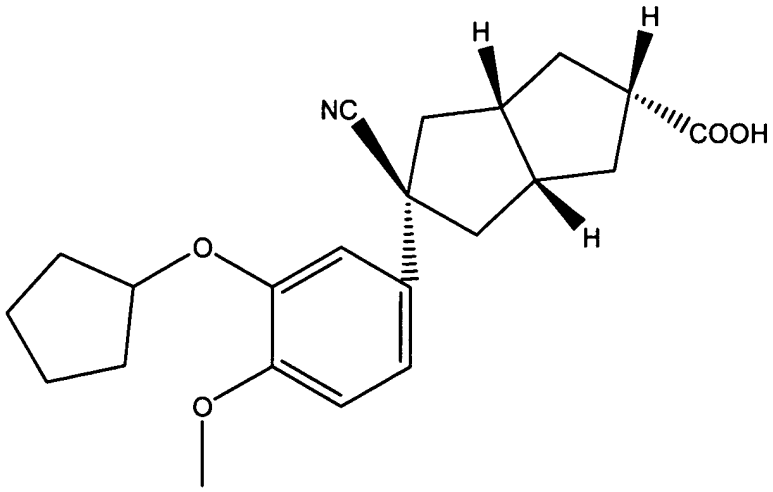
With regard to PDE4 inhibitors in particular, an extraordinary degree of unpredictability also existed in the state of the prior art regarding how the modification of various chemical substituents bound to previously known PDE4 inhibitors would dramatically affect the biological activity characteristics thereof. This uncertainty is directly attributable to a distinct lack of knowledge of the skilled artisan with respect to being able to accurately extrapolate how minor, seemingly trivial, structural modifications to an active core compound of an already known inhibitor of PDE4 can create profound changes in the inhibitory characteristics thereof. This extraordinary degree of unpredictability, due to the paramount and unpredictable ramifications that minor structural can have on the characteristics of PDE4 inhibition, is particularly evidenced by a scientific journal article, namely Ochiai, H., et al., "Orally Active PDE4 Inhibitor with Therapeutic Potential," *European Journal of Medicinal Chemistry*, Vol. 39, pp. 555-571 (2004), which stated that upon derivatizing Ariflo (a.k.a., Cilomilast or SB-207499) with different stereoisomers of bicyclo[3.3.0]octane (chemical structures provided hereinbelow), the (*2r,5r*)-bicyclo[3.3.0]octane derivative of Ariflo was an astonishing seventeen-fold more efficacious inhibitor of LPDE4 activity than the (*2s,5r*)-bicyclo[3.3.0]octane derivative of Ariflo. Moreover, the inhibitory characteristics of (*2r,5s*)-bicyclo[3.3.0]octane were surprisingly inverted in that said derivative exhibited negligible inhibition relative to the extremely active (*2r,5r*)-bicyclo[3.3.0]octane derivative of Ariflo!



(2*s*,3a*S*,5*r*,6a*R*)-5-cyano-5-(3-(cyclopentyloxy)-4-methoxyphenyl)-octahydropentalene-2-carboxylic acid (a.k.a., (2*s*,5*r*)-bicyclo[3.3.0]octane derivatized Ariflo)

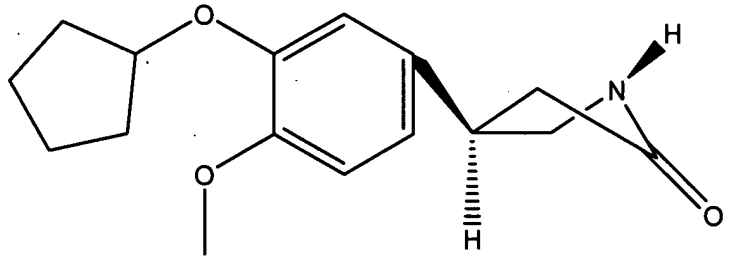


(2*r*,3a*S*,5*r*,6a*R*)-5-cyano-5-(3-(cyclopentyloxy)-4-methoxyphenyl)-octahydropentalene-2-carboxylic acid (a.k.a., (2*r*,5*r*)-bicyclo[3.3.0]octane derivatized Ariflo)
seventeen-fold more potent inhibitor relative to (2s,5r)-bicyclo[3.3.0]octane derivatized Ariflo

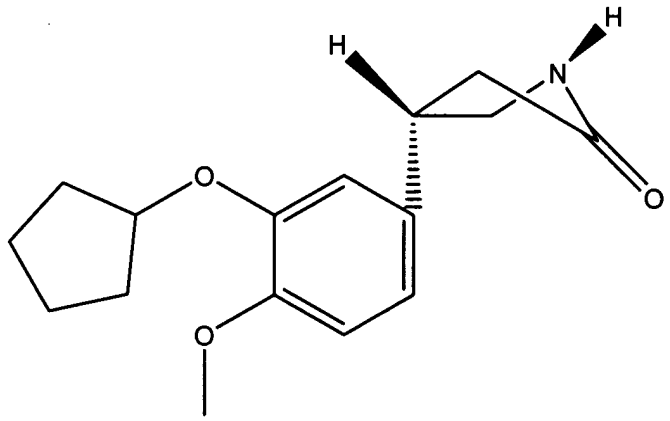


(2*r*,3a*S*,5*s*,6a*R*)-5-cyano-5-(3-(cyclopentyloxy)-4-methoxyphenyl)-octahydropentalene-2-carboxylic acid (a.k.a., (2*r*,5*s*)-bicyclo[3.3.0]octane derivatized Ariflo)
negligible inhibitory efficacy relative to (2r,5r)-bicyclo[3.3.0]octane derivatized Ariflo

This phenomena of unpredictability is further evidenced by a scientific journal article, namely Christensen, S.B., et al., "1,4-Cyclohexanecarboxylates: Potent and Selective Inhibitors of Phosphodiesterase 4 for the Treatment of Asthma," *Journal of Medicinal Chemistry*, Vol. 41, pp. 821-835 (1998), which stated that (R)-Rolipram was approximately a four-fold more efficacious inhibitor of LPDE4 activity than (S)-Rolipram.

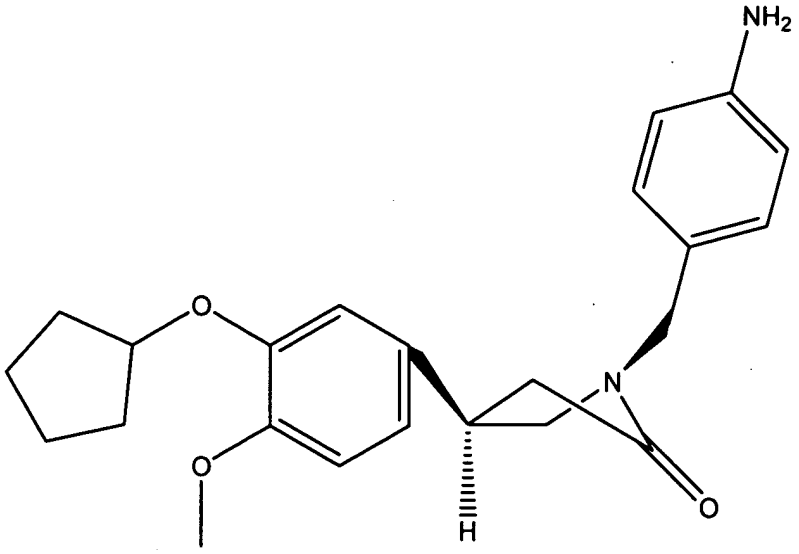


(*R*)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one (a.k.a., (R)-Rolipram)
four-fold more potent inhibitor relative to (S)-Rolipram

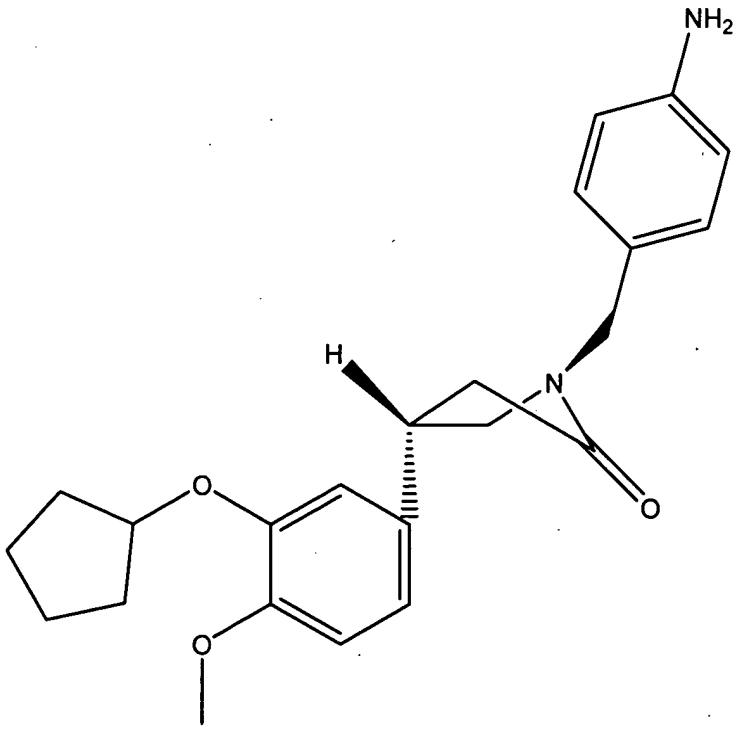


(*S*)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one (a.k.a., (S)-Rolipram)

Surprisingly however, upon derivatizing each of the aforementioned stereoisomers with an N-(4-aminobenzyl) substituent, the 4-aminobenzyl derivative of (S)-Rolipram alternatively demonstrated not only a four-fold improvement in LPDE4 inhibition relative to the 4-aminobenzyl derivative of (R)-Rolipram, but also a dramatic six-fold improvement in LPDE4 inhibition relative to the underivatized (R)-Rolipram.



(*R*)-1-(4-aminobenzyl)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one
(a.k.a., 4-aminobenzyl derivatized (R)-Rolipram)



(*S*)-1-(4-aminobenzyl)-4-(3-(cyclopentyloxy)-4-methoxyphenyl)pyrrolidin-2-one
(a.k.a., 4-aminobenzyl derivatized (S)-Rolipram)
four-fold more potent inhibitor relative to the 4-aminobenzyl derivatized (R)-Rolipram
six-fold more potent inhibitor relative to the underivatized (R)-Rolipram

In general, the basis for the extraordinary degree of unpredictability associated with all of the previously discussed unexpected scientific experimental results can be directly attributed to the exquisite stereospecificity that exists between an enzyme and its corresponding substrate, and a ligand and its corresponding receptor. As a result, one of ordinary skill in the art would not be able to reasonably predict or anticipate the ramifications that minor structural changes, with respect to different stereoisomers of a core compound, can have on the bioactive properties thereof.

With respect to the aforementioned discussion regarding PDE4 inhibitors in particular, it is readily apparent that one of ordinary skill in the art would not be able to accurately extrapolate how minor structural changes of various chemical substituents associated with stereoisomers of a previously known PDE4 inhibitor would affect the inhibitory characteristics thereof. This begs the question, if one of ordinary skill in the art could not reasonably anticipate how the relative inhibitory characteristics would be influenced by altering the various chemical substituents associated with stereoisomers of an already known PDE4 inhibitor (i.e., Ariflo and Rolipram), then how could one of ordinary skill in the art reasonably predict how the selectivity and efficacy characteristics of PDE4 inhibition would be influenced by modifying the instant substituted indazole in accordance with the vast number of potential derivates thereof? It would therefore be logical to conceive and envision that the difficulties previously encountered with respect to predicting how inhibition would be influenced by changing various chemical substituents bound to stereoisomers of conventional PDE4 inhibitors, would reasonably be compounded and thus prove to be even more troublesome for one of ordinary skill in the art attempting to modify the instant PDE4 inhibitor, while maintaining selective inhibitory characteristics thereof.

Moreover, the instant application is directed to a substituted indazole and a seemingly infinite number of potential chemical moieties that may constitute not only a single pendant R, R^1, R^2_a and R^2_b group, but

also the R^{500} potential substituents thereof. Based on the breathtaking scope of the claimed invention and the extraordinary degree of unpredictability associated therewith, a skilled artisan would quickly become overburdened with the daunting task of attempting to accurately predict which of the countless number of derivatives, if synthesized, would actually exhibit selective inhibition of all PDE4 isozyme subtypes. Without more, such as scientific data illustrating structure-activity relationships with respect to how the actual substitution of the generic indazole with various particular chemical moieties directly impacts the selective inhibition against PDE4 and specific isozyme subtypes thereof, one of ordinary skill in the art would not be able to extrapolate, without an undue amount of experimentation, which of the exponential number of derivatives disclosed across the entire breadth of the tremendously broad claims would in fact actually exhibit selective inhibitory properties against even a single PDE4 isozyme subtype thereof, sufficient to restore normal gastric motility. As a result, a skilled artisan seeking to practice the extraordinary scope of the claimed subject matter would be required to perform an extraordinary amount of trial and error experimentation (i.e., inhibition assays) to identify inhibitors of PDE4. Therefore, it would be utterly impossible to practice the entire scope of the claimed invention as the skilled artesian would not know, or even begin to be able to accurately predict, which of the vast number of derivatives would in fact exhibit selective inhibition commensurate with the full scope of the claims. In conclusion, due to the extraordinary degree of unpredictability in the art at the time the instant application was filed with respect to accurately extrapolating how minor structural changes of various chemical substituents associated with stereoisomers of a PDE4 inhibitor can dramatically affect the inhibitory characteristics thereof, one of ordinary skill in the relevant art would not be able use the invention commensurate in scope with the aforementioned rejected claims.

6. The amount of guidance or direction provided by the inventor

The "amount of guidance or direction" refers to the information present within the application as originally filed that teaches one skilled in the art exactly how to make and use the invention. MPEP § 2164.03. The amount of guidance or direction that is required in the specification to enable the invention is inversely proportional not only to the amount of knowledge present in the state of the art, but also to the level or degree of predictability in the art, as of the effective filing date of the application. *In re Fisher*, at 24. MPEP §§ 2164.03, 2164.05(a).

As previously discussed, a great deal of uncertainty due to a distinct lack of knowledge of the skilled artisan existed in the state of the art at the time the instant application was filed. Furthermore, as of the effective filing date of the instant application, there was an extremely low level or degree of predictability in the art. Therefore, the applicant was required to provide in the specification additional detail directed to how to make and use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention.

Although the instant specification provides a method that *may* be utilized to determine the relative ability of the inhibitors to inhibit PDE4, absolutely no indication of the actual bioactivity of any of the claimed substituted indazoles is disclosed. In addition, no method or guidance is provided directing one of ordinary skill in the art as to what particular steps need be performed to measure the activity against even a single particular PDE4 isozyme type and subtype thereof, despite the fact that applicants' explicitly assert in their specification (page 55, line 35; and page 56, lines 1-3) that *all PDE4 isozyme types and subtypes thereof* are included within the scope of their invention with respect to inhibiting PDE4 isozyme activity. Therefore, since not even a scintilla of *in vivo* test data is presented illustrating the actual relative selectivity and efficacy of their broadly claimed inhibitors of PDE4, the therapeutic utility of these compounds are

obviously extremely difficult to assess. See "Substituted Indazole Derivatives and their Use as Inhibitors of PDE4," Expert Opinion on Therapeutic Patents, Vol. 8, No. 8, pp. 1053-1056, Ashley Publications Ltd. (1998).

Aside from merely providing a handful of general schematic methods undertaken to prepare only a small portion of the chemical derivatives claimed, the specification is completely devoid of any guidance or direction on how to go about selecting even a scintilla of the countless number of possible chemical derivatives encompassed by the seemingly all-embracing scope of the claimed invention. Furthermore, if one skilled in the art contemplating which of the vast number of derivates to synthesize were to turn to the specification for guidance in an effort to gain insight on how the structural differences between the aforementioned derivatives may influence or directly impact the selective inhibition of PDE4, one would unfortunately find a complete lack and total absence of even a scintilla of scientific data illustrating that inhibition is in fact demonstrated by even a single purported inhibitor of PDE4. Therefore, although the instant application discloses a vast number of chemical derivatives, the specification fails to provide sufficient guidance to the skilled artesian with respect to a means for determining (i.e., structure-activity relationship data) which particular derivatives would in fact exhibit selective inhibition against PDE4 isozymes, as well as subtypes thereof, with respect to the full scope of the claims.

*7. **The presence or absence of working examples***

The need that working examples be present in the specification in order to enable the invention is inversely proportional not only to the amount of knowledge present in the state of the art, but also to the level or degree of predictability in the art. MPEP § 2164.02.

Since only an enabling disclosure is required, the applicant need not provide working examples of all actual embodiments of the claimed invention. *Id.* In fact, the mere presence of only a single working

example should never be the sole reason for rejecting claims as being broader than the enabling disclosure of the specification. *Id.* Moreover, the specification need not necessarily contain even a single working example, so long as the claimed invention is otherwise disclosed in the specification in such a manner that one of ordinary skill in the art would be able to practice the invention without an undue amount of experimentation. *In re Borkowski*, 164 USPQ 642, 645 (CCPA 1970). However, the utter lack of even a single working example, as well as a complete absence of evidence supporting that the claimed invention does in fact work as described, are certainly considerations that must be taken into account along with the other Wands factors, especially in cases involving unpredictable arts, such as most chemical reactions and physiological activities. MPEP § 2164.02. As a result, a rejection stating that enablement is limited to a particular scope due to a lack of working examples or a lack of evidence supporting that the claimed invention does in fact work as described may therefore be appropriate. *Id.*

The instant specification merely provides the chemical names and structures of only a small portion of the chemical derivatives claimed, despite the fact that over ninety-one (91) entire pages in length are solely directed to defining a seemingly infinite number of various chemical moieties that may constitute not only the pendant R, R^1, R^2_a and R^2_b groups, but also R^{500} potential substituents thereof. Although the examiner recognizes that the specification need not necessarily disclose the method of making and using each and every chemical derivative that exhibits PDE4 inhibition as claimed, a reasonable fraction of working embodiments is however required. This is especially the case, when one of ordinary skill in the biotechnology, chemical and pharmaceutical arts would not reasonably be expected to be able to extrapolate the disclosure of only a small number of professed working embodiments across the entire scope of the tremendously broad claims. In addition, of the small portion of chemical derivatives that are disclosed, the instant specification provides absolutely no scientific data illustrating that inhibition of even a single alleged

PDE4 inhibitor. Without a representative correlation between how variations in chemical structure directly impact PDE4 inhibition, the skilled artesian would be overburdened with trying to predict, by extrapolation of only a small portion of chemical derivatives, which of the infinite number of derivatives disclosed across the entire scope of the extremely generic claims would actually exhibit inhibition against PDE4, including all isozyme subtypes thereof.

8. The Quantity of Experimentation Required to Make and Use the Claimed Invention Based Upon the Content of the Supporting Disclosure

The quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure is directed to whether necessary experimentation that is required for practicing the invention would be reasonably considered to be "undue." MPEP § 2164.06.

Although the presence of inoperative embodiments within the scope of the claim does not in and of itself necessarily render a claim non-enabled, if the number of inoperative combinations becomes significantly large, and has the effect of forcing one of ordinary skill in the art to conduct an unduly amount of experimental research in order to practice the full scope of the claimed invention, then the claims might indeed be invalid for failing the statutory requirement as set forth in 35 U.S.C., 112, first paragraph. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (Fed. Cir. 1984).

Based on the immense scope of the aforementioned claims, especially when considered in light of the lack of supporting disclosure within the specification, said claims overwhelming exceed the enablement provided by the specification. Therefore, it would be impossible for one of ordinary skill in the art to reasonably and accurately predict *a priori* from the specification and chemical moieties disclosed therein, which chemical derivatives would in fact exhibit selective inhibition against PDE4, including all isozyme

subtypes thereof. As a result, a significant amount of undue trial and error experimentation would therefore be required to identify inhibitors of PDE4.

As previously discussed hereinabove, there was an extraordinary lack of predictability in the art at the time the instant application was filed. In addition, not only was there a complete lack and total absence of even a scintilla of scientific data illustrating that inhibition is in fact demonstrated by even a single purported inhibitor of PDE4, the specification also failed to provide any guidance as to a means for determining or predicting (i.e., structure-activity relationships) which particular chemical derivatives would reasonably be expected to exhibit selective inhibitory characteristics of PDE4 and isozyme subtypes thereof following an actual synthesis of said chemical derivative. Given the breathtaking scope of the claimed invention and the requirement that each derivative must be synthesized and tested individually, determining which of the numerous embodiments were merely conceived by the applicants and therefore claimed but not yet actually synthesized and verified as to whether they in fact exhibit specific inhibition of PDE4, would clearly require undue experimentation on behalf of one of ordinary skill in the art attempting to practice entire scope of the invention as claimed. In conclusion, the specification does not enable the skilled artesian to use the invention commensurate in scope with the aforementioned rejected claims.

37 C.F.R. 1.105 Requirement for Information

Recently the CAFC affirmed that a patent examiner, on behalf of the USPTO may require, pursuant to 37 C.F.R. 1.105, the production of information that is "reasonably necessary to properly examine or treat the matter." *Star Fruits S.N.C. v. United States*, 73 USPQ 2d 1409 (CAFC 2005). As a result, the USPTO may require the submission of information that is either "material to patentability," in accordance with 37 C.F.R. 1.56, or "reasonably calculated to lead to such relevant information," in accordance with 37 C.F.R. 1.105, which is therefore broader in scope than 37 C.F.R. 1.56. Consequently, the applicant and the assignee

of this application are required under 37 CFR 1.105 to provide the following information that the examiner has determined is reasonably necessary for the purpose of evaluating the proper scope of enablement.

1. The examiner is respectfully requesting that the applicant and the assignee of the instant application provide the USPTO with scientific experimental data and research results that were actually acquired and are pertinent to illustrating the relative inhibition, ***as well as a lack thereof***, against PDE4 and isozyme subtypes thereof demonstrated by ***All*** of the derivatives disclosed and claimed across the entire scope of the extremely broad claims, which were in fact synthesized and tested for inhibition. The scientific experimental data and research results are being requested in an effort to determine whether a significant percentage of the derivatives disclosed and claimed across the entire scope of the tremendously broad and extremely generic claims are in fact biologically active (i.e., exhibit selective inhibition against PDE4 and isozyme subtypes thereof) as claimed by the applicant.

2. In addition, the examiner is also respectfully requesting that the applicant and the assignee of the instant application provide the USPTO with the corresponding chemical structures of all of the derivatives for which enzyme inhibition data are available. The corresponding chemical structures are being requested to aid in determining the issue of enablement with respect to the generic claims and the instant specification.

In responding to an official requirement for information that necessitate the submission by the applicant of copies of documents, which are bound a text or a single article over 50 pages in length, the requirement may be met by providing copies of only those relevant pages that provide the particular subject matter indicated in and pertinent to the requirement.

The applicants are respectfully reminded that a duty of candor and good faith, under 37 CFR 1.56, applies to the applicants' reply to an official requirement for information under 37 CFR 1.105.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112, which forms the basis of the claim rejections as set forth under this particular section of the Official Action:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 42-44 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, each of said claims recite "an inhibitor of phosphodiesterase-4 (PDE4), including isozyme subtypes thereof." In addition, the specification states (page 56, lines 1-3) that the expression "inhibit PDE4 isozyme activity" is intended to mean "all types and subtypes of PDE4 isozymes." There are at least eleven known families or classes of PDE inhibitors, wherein PDE4 contains four specific isozyme subtypes, namely PDE4A, PDE4B, PDE4C and PDE4D. It is unclear whether the claim recitation "an inhibitor of phosphodiesterase-4 (PDE4), including isozyme subtypes thereof" is directed to any, at least one or "all" (as supported by the specification) PDE4 isozyme subtypes. Appropriate clarification is required.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 102, which forms the basis of the anticipation rejections as set forth under this particular section of the Official Action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 31, 36-39 and 44 are rejected under 35 U.S.C. § 102(b) as being anticipated by the International Patent Application WO 97/42174 (hereinafter "WO '174"), which was filed by the assignee Pfizer on behalf of the inventor Marfat and subsequently published on November 13, 1997. The instant application claims benefit to a provisional patent application (Serial Number: 60/114,217), which was filed on December 30, 1998.

Independent claim 44, and dependent claims 31 and 36-39 of the instant application are directed to a pharmaceutical composition comprising an inhibitor of phosphodiesterase-4 (PDE4) for therapeutically treating or preventing stasis or hypomotility in the stomach (a.k.a., gastroparesis), the elected species of which is cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid.

Similarly, WO '174 discloses a pharmaceutical composition comprising the same inhibitor of PDE4, namely cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid. The claim recitation of the instant invention that is directed towards therapeutically treating or preventing stasis or hypomotility in the stomach will be given little probative patentable weight as such a recitation is merely directed towards methods of intended future use, which does not impact the structure of said PDE4 inhibitor. When a claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. See *In re May*, 197 USPQ 601, 607 (CCPA 1978). Furthermore, a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967); and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963).

Moreover, the "discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." See *Atlas Powder Co. v. Ireco Inc.*, 51 USPQ 2d 1943, 1947 (Fed. Cir. 1999). Therefore, merely claiming a new use, new function or unknown property, which is inherently present in the prior art, does not necessarily make the claim patentable. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977); and MPEP § 2112. Furthermore "products of identical chemical composition can not have mutually exclusive properties," since a chemical composition and its properties are inseparable. See *In re Spada*, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990); and MPEP § 2112. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. See MPEP § 2112.

2. Claims 1-2, 7-10, 16-18, 20, 25-27 and 42-43 are rejected under 35 U.S.C. § 102(b) as being anticipated by WO '174.

Independent claim 1, and dependent claims 2 and 7-10 of the instant application are directed to a method of treating or preventing stasis in the stomach comprising administering a therapeutically effective amount of an inhibitor of phosphodiesterase-4 PDE4, the elected species of which is cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid. In addition, independent claim 42 and dependent claims 16-18, as well as independent claim 43 and dependent claims 20 and 25-27, of the instant application are directed to a method of treating or preventing gastric or gastrointestinal disorder comprising administering a therapeutically effective amount of an inhibitor of PDE4, the elected species of which is cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid.

Similarly, WO '174 discloses a method of treating or preventing Crohn's disease, inflammatory bowel disease, ulcerative colitis and diabetes mellitus comprising administering a therapeutically effective

amount of the same inhibitor of PDE4 (abstract; page 8, line 30; page 9, lines 8-9; page 10, lines 1-26; page 41, lines 27-28; and claims 11, 19 and 20).

As previously discussed, by treating or preventing diabetes mellitus by inhibiting PDE4 via administration of a therapeutic composition comprising the same PDE4 inhibitor, namely cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid, one would also be inherently treating or preventing the secondary condition, namely gastroparesis, which develops during the course of the primary disease diabetes mellitus.

"Stasis" is defined as a slowing or stoppage of the normal flow of a bodily substance, such as intestinal contents through the bowels. See Dictionary.com's definition for "stasis" at the following internet address (URL: http://dictionary.reference.com/search?q=stasis). In addition, gastroparesis is commonly caused by, and is often seen as a complication of, diabetes mellitus. More specifically, "gastroparesis" is a secondary condition of diabetes mellitus in which there is delayed stomach emptying due to abnormal gastric motility (i.e., hypomotility). See CancerWeb's online definition for "gastroparesis" at the following internet address (URL: http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=gastroparesis&action=Search+OMD), a printout of which is provided for your convenience.

This rationale is further echoed by the applicants' own admissions in which applicants explicitly proclaim in their Election, which was filed on April 12, 2004, that "disorders treated by the compounds of the present application prevent or treat hypomotility in the stomach and any gastrointestinal disorders resulting therefrom. Thus, hypomotility and the resulting gastrointestinal disorders are cause and effect of the same physical condition." See page 4, lines 5-8. Applicants also declare that "it is not possible for the issue of hypomotility in the stomach to be divorced from the gastrointestinal illnesses and conditions the prevention and treatment of which are the subject of the claims of the present application." See page 4, lines

14-15. Furthermore, Applicants explicitly profess that "it is not seen how treatment or prevention of stasis in the stomach, on the one hand, and treatment or prevention of a gastric or gastrointestinal disorder, on the other, which each employ the identical method, are independent and distinct of each other." See page 5, lines 4-7. Photocopies of relevant portions of the above referenced Election are provided herein for your convenience. Applicants' own acknowledgement of the inseparable nature of a secondary condition (i.e., gastric stasis or hypomotility), which is a direct result of a primary illness (i.e., gastrointestinal disorder), is equally applicable to the secondary condition of gastroparesis, which arises as a complication of the primary disease diabetes mellitus.

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103. See MPEP § 2112. This same rationale should also apply to product and process claims claimed in terms of function, property or characteristic. *Id.* Where the claimed and prior art products are identical or substantially identical in structure or composition a prima facie case of either anticipation or obviousness has been established. See *In re Best*, 195 USPQ 430, 433 (CCPA 1977). Therefore, the prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *Id.* "The PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on 'prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same." See *In re Fitzgerald*, 205 USPQ 594, 596 (CCPA 1980) (quoting *In re Best*, 195 USPQ 430, 433-34 (CCPA 1977)).

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of the appropriate paragraph of 35 U.S.C. § 103, which forms the basis of the obviousness rejections as set forth under this particular section of the Official Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1-2, 7-10, 16-18, 20, 25-27, 31, 36-39 and 42-44 are rejected under 35 U.S.C. § 103(a) as being obvious in light of the combined teachings of WO '174 and the International Patent Application WO 94/06423 (hereinafter "WO '423"), which claims priority to the same two German Patent Documents (Serial Number: DE 42 30 755.4, Filed: September 14, 1992; and Serial Number: DE 43 24 571.4; Filed July 17, 1993), as U.S. Patent Number 5,891,904, which issued to Stief et al. on April 6, 1999.

Claims 1-2, 7-10, 16-18, 20, 25-27, 31, 36-39 and 42-44 of the instant application are collectively directed to a pharmaceutical composition and methods of treating or preventing gastric stasis and gastrointestinal disorders comprising administering a therapeutically effective amount of an inhibitor of PDE4, the elected species of which is cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid.

Similarly, WO '174 teaches administering a therapeutically effective amount of an inhibitor of PDE4, namely cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid (abstract; page 9, lines 8-9; page 10, lines 1-26; page 41, lines 27-28; and claims 11, 19 and 20). It would have been obvious to one of ordinary skill in the art to utilize the PDE4 inhibitor, namely cis-4-cyano-4-(1-cyclohexyl-3-ethyl-

1*H*-indazol-6-yl)cyclohexanecarboxylic acid, as taught in WO '174 reference to treat motility issues associated with the gastrointestinal tract, as taught by the WO '423 reference. Sufficient motivation to do so exists, as the WO '423 reference explicitly states that inhibitors of PDE4 are highly effective therapeutic agents for the modulation of gastric motility and peristalsis (page 1, lines 1-8; page 2, lines 14-37; and page 3, lines 1-3), and the WO '174 reference explicitly teaches only eleven "preferred" indazole compounds as inhibitors of PDE4, the seventh of which is specifically defined as "cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid." A reasonable expectation of success in combining the aforementioned references is present as it was known by those skilled in the art that cis-4-cyano-4-(1-cyclohexyl-3-ethyl-1*H*-indazol-6-yl)cyclohexanecarboxylic acid inhibits PDE4 and that PDE4 inhibitors are highly effective therapeutic agents for the modulation of gastric motility and peristalsis.

2. Claims 28 and 29 are rejected under 35 U.S.C. § 103(a) as being obvious in light of the combined teachings of: WO '174 and WO '423; and in further view of U.S. Patent Number 5,804,595, which issued to Portoghese et al. on September 8, 1998 (hereinafter the "Portoghese et al. '595 patent"), and U.S. Patent Number 4,785,000, which issued to Kreek et al. on November 15, 1988 (hereinafter the "Kreek et al. '000 patent").

Claims 28 and 29 of the instant application are directed to a pharmaceutical composition comprising not only an inhibitor of PDE4, which therapeutically treats or prevents gastroparesis, but also an opioid analgesic, which includes selective and nonselective agonists and antagonists of μ, κ and δ opioid receptors.

Neither WO '174, nor WO '423 disclose combining a PDE4 inhibitor with an opioid analgesic. However, the Portoghese et al. '595 patent teaches a method of utilizing a therapeutic compound comprising a selective κ opioid receptor agonist useful for alleviating pain and suffering inflicted by chronic inflammatory diseases such as gastrointestinal motility disorders, wherein said agonist can produce analgesia

without the dependence and respiratory depression associated with μ opioid receptor activation by morphine (column 1; lines 30-33; and column 4; lines 20-30). Furthermore, the Kreek et al. '000 patent teaches a method of utilizing a therapeutic composition comprising an opioid analgesic, such as morphine, and an opioid antagonist, wherein said composition is useful for alleviating or preventing pain caused by intestinal hypomotility (column 1; lines 1-25, 34-36, 42-45 and 52-61; column 2, lines 38-60; and column 3, lines 1-8 and 43-46).

It would have been obvious to one of ordinary skill in the art to administer an opioid analgesic, such as a selective or nonselective agonist or antagonist of μ, κ and δ opioid receptors, as taught by the Portoghese et al. '595 and Kreek et al. '000 patents, concomitantly with an inhibitor of PDE4, as taught by WO '174 and WO '423, so at to alleviate or prevent pain associated with inflammatory bowel disease and gastroparesis while treating or preventing not only Crohn's disease, inflammatory bowel disease and ulcerative colitis, but also diabetes mellitus.

Conclusion

Claims 3-6, 12-15, 21-24 and 32-35 were withdrawn from consideration. Claims 40 and 41 were cancelled. Claims 11, 19 and 30 were cancelled and replaced with new claims 42, 43 and 44. Claims 1-2, 7-10, 16-18, 20, 25-29, 31, 36-39 and 42-44 are rejected.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David P. Stitzel, Esq. whose telephone number is 571-272-8508. The examiner can normally be reached on Monday-Friday, from 7:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary L. Kunz can be reached at 571-272-0887. The central fax number for the USPTO is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published patent applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished patent applications is only available through Private PAIR. For more information about the PAIR system, please see http://pair-direct.uspto.gov. Should you have questions about acquiring access to the Private PAIR system, please contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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